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# Amyloid in intervertebral discs of surgery and autopsy material

## A new class of amyloid?

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**Summary.** Intervertebral discs from 82 consecutive operations on herniation and 59 autopsies (one case with generalized amyloidosis) were studied. Amyloid deposits observed in surgical and autopsy specimens increased with age in both series. Degenerative changes were related to age and to amyloid deposits in autopsy, but not in surgical cases. Calcium pyrophosphate dihydrate deposits (often in proximity to amyloid deposits) were found in autopsy discs of six patients and in surgical specimens of three patients with previous operations on herniated discs.

Antisera against amyloid fibril proteins of different types including AA-, Aλ-, Aκ, AF- and AB-types showed no reaction with disc amyloid. In one case with generalized Aλ-amyloidosis the disc amyloid was not of the Aλ-type.

Based on our results, we suppose that disc amyloid is a form of localized senile amyloidosis – possibly representing a new class of amyloid limited to cartilage tissue.

**Key words:** Amyloidosis – Immunohistochemistry – Intervertebral disc

## Introduction

There has been little study of the presence of amyloid in intervertebral discs following the first report of deposits of amyloid in discs by Virchow (1855). Bywaters and Dorling (1970) and Ballou et al. (1976) described the occurrence of amyloid deposits in the discs of patients suffering from generalized amyloidosis, further studies having demonstrated amyloid deposits in discs of laboratory animals (Shimizu et al. 1982), in surgically removed herniated human disc specimens (Wagner and Mohr 1984; Takeda et al. 1984; Ladefoged et al. 1986) and in human intervertebral discs obtained from randomly selected autopsies (Ladefoged 1985) – see also Ryan (1986) for a review.

The aim of our investigation was to correlate the amount and frequency of amyloid deposits with age, degenerative changes and deposits of calcium pyrophosphate dihydrate (CPPD). We also studied the intervertebral discs of a patient with generalized amyloidosis and, in addition, examined the amyloid of 13 discs with immunohistological techniques, using antibodies against the known major amyloid types.

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## Materials and methods

We studied intervertebral discs from 141 patients. In 82 cases (average age of patients: 49.1 years, range: 23–93 years), the disc tissue originated from consecutive operations on herniated discs (Department of Neurosurgery, University of Hamburg, FRG). Due to the operation technique the surgically removed material consisted of a large number of small pieces.

In 58 cases (average age of patients: 51.4 years, range: 23–94 years) and in one case of the patient with generalized amyloidosis, intervertebral discs (L3/L4, L4/L5, L5/S1) were obtained from autopsies (Department of Pathology, Marienkrankenhaus Hamburg 35 cases, Institute of Pathology, University of Hamburg 1 case, and the Institute of Forensic Medicine, University of Hamburg 23 cases). None of these patients had previously undergone surgery for herniated discs. The autopsy discs were removed in one piece and cut in a manner to preserve macroscopically both of annulus fibrosus and nucleus pulposus in the preparated piece.

The surgical specimens were immediately fixed after removal for at least 96 h in 4% buffered formalin. Fixation of the autopsy specimens could only be started 51.9 h (range: 25–79 h) post mortem. After dehydration and embedding in paraffin (two blocks per disc), 3 μm thick sections were stained with haematoxylin-eosin and Congo red according to Puchtler et al. (1962). Amyloid was considered to be present when the Congo

**Table 1.** Categories of amyloidosis and degeneratives changes

| Degree of severity | Amyloidosis | Degenrative changes |
|---|---|---|
| 0 = absent | no amyloid | no degenerative changes |
| I = mild | amyloid deposits in one to four visual fields[a] | degenerative changes in one to four visual fields[a] |
| II = moderate | amyloid deposits in five to eight visual fields[a] | degenerative changes in five to eight visual fields[a] |
| III = severe | amyloid deposits in more than eight visual fields[a] | degenerative changes in more than eight visual fields[a] |

[a] obj. 10:1

red stained material showed green bireringence in polarized light.

The frequency of fissures accompanied by proliferation of chondrocytes was considered to be the most important criterion among the changes seen (e.g. fibrillation, fibrosis in nucleus pulposus, ossification) related to cartilage degeneration. It was therefore used for grading.

The degree of severity (Table 1) of amyloidosis and degenerative changes were scored after having examined the specimens (squares 1,5 x 1,5 cm per block) systematically under a 10:1 microscope objective.

For the immunohistological procedure and the potassium permanganate method (Wright et al. 1977) we chose specimens from ten discs with large amyloid deposits, five out of each group (surgery and autopsy). In addition, we tested three discs (L3/L4, L4/L5, L5/S1), heart, spleen and kidney from the patient with generalized amyloidosis. The primary antibodies consisted of a mouse monoclonal antibody (mc1) against amyloid A (Linke 1984) (dilution 1:20, PAP-technique), rabbit polyclonal antibodies against prealbumin-derived amyloid (Linke 1982) (dilution 1:500, PAP), light chain amyloid of the kappa type (Linke 1982) and lambda type (Eulitz and Linke 1985; Linke et al. 1986) (dilutions 1:400 and 1:600, ABC-technique) and human-$\beta_2$-microglobulin (Dakopatts Co., D-2000 Hamburg) (dilution 1:200, ABC). The latter was used to identify amyloid (AB type) in patients on long-term haemodialysis. Conventional positive and negative controls were prepared. We considered the immunohistological reaction to be positive when the immunohistochemical reaction product (substrat: $H_2O_2$, chromogene: diaminobenzidine) was congruent with the amyloid deposits defined by Congo red staining.

The chi-square-test was used for statistical evaluation.

## Results

Amyloid deposits were observed in the annulus fibrosus between collagen bundles and in the nucleus pulposus in a more nodular scattered form, often in a half-moon or corona like shape in close proximity to chondrocytes (Fig. 1 and Fig. 2).

Table 2 shows the relationship between the amount of amyloid deposit and the age of patients. Moderate and severe deposits of amyloid were found mainly in the disc specimens of the older cases. In only a few cases in younger patients were small amounts of amyloid deposits found in the discs. A statistically significant correlation ($p < 0.001$) was found for location of amyloid at L3/L4, L4/L5 and L5/S1 in the autopsy specimens (Table 2A) and for L4/L5 but not for L5/S1 ($p > 0{,}05$) in the surgically removed material (Table 2B). A positive correlation was also found for the total of examined surgery specimens, independent of disc location (Table 2B).

Furthermore, we found that degenerative changes of autopsy discs (Table 3A) increase with age ($p < 0.01$ (L3/L4), $p < 0.001$ (L4/L5, L5/S1)). No such statistical significance ($p > 0.05$) could be shown for the surgical specimens (Table 3B).

Degenerative changes and amyloid deposits were positively correlated ($p < 0.001$) in autopsy disc specimens (Table 4A) but not in those from herniated discs ($p > 0.05$) (Table 4B).

In the autopsy material (58 patients) CPPD (Fig. 3) was detected in six cases (average age of patients: 65.7 years, range 56–75 years), in at least one of the three examined intervertebral discs in the form of rhomboid or rod-shaped variably birefringent crystals. In these cases we found amyloid deposits in 12 of 13 discs containing CPPD.

Eight of the 82 patients operated on for herniation had undergone prior surgery in the same intervertebral space. Amyloid was seen in all of these cases. CPPD was found only in the disc sections of three patients (average age of patients: 49 years, range: 43–55 years) who had undergone surgery before for herniation.

Immunohistologically, we failed to state a positive reaction with the antibodies used (anti-AA, anti-A$\lambda$, anti-A$\kappa$, anti-AF, anti-$\beta_2$-microglobulin).

The material of the case with generalized amyloidosis was obtained from a 47-year-old man. The patient had no detectable monoclonal protein in serum or urine. He died from congestive heart failure. Histopathologically, moderate to severe amyloid deposits were found in heart, spleen, kidney, liver, lung, pancreas, rectum, oesophagus, prostate, skin, lymph nodules, skeletal muscles, adrenal gland, aorta, gallbladder, and pituitary gland. There was no amyloid in the brain. In discs we found amyloid deposits from mild to moderate degree. The immunohistological examination of tissue specimens from heart, spleen and kidney showed an amyloidosis of the A$\lambda$-type. The discs

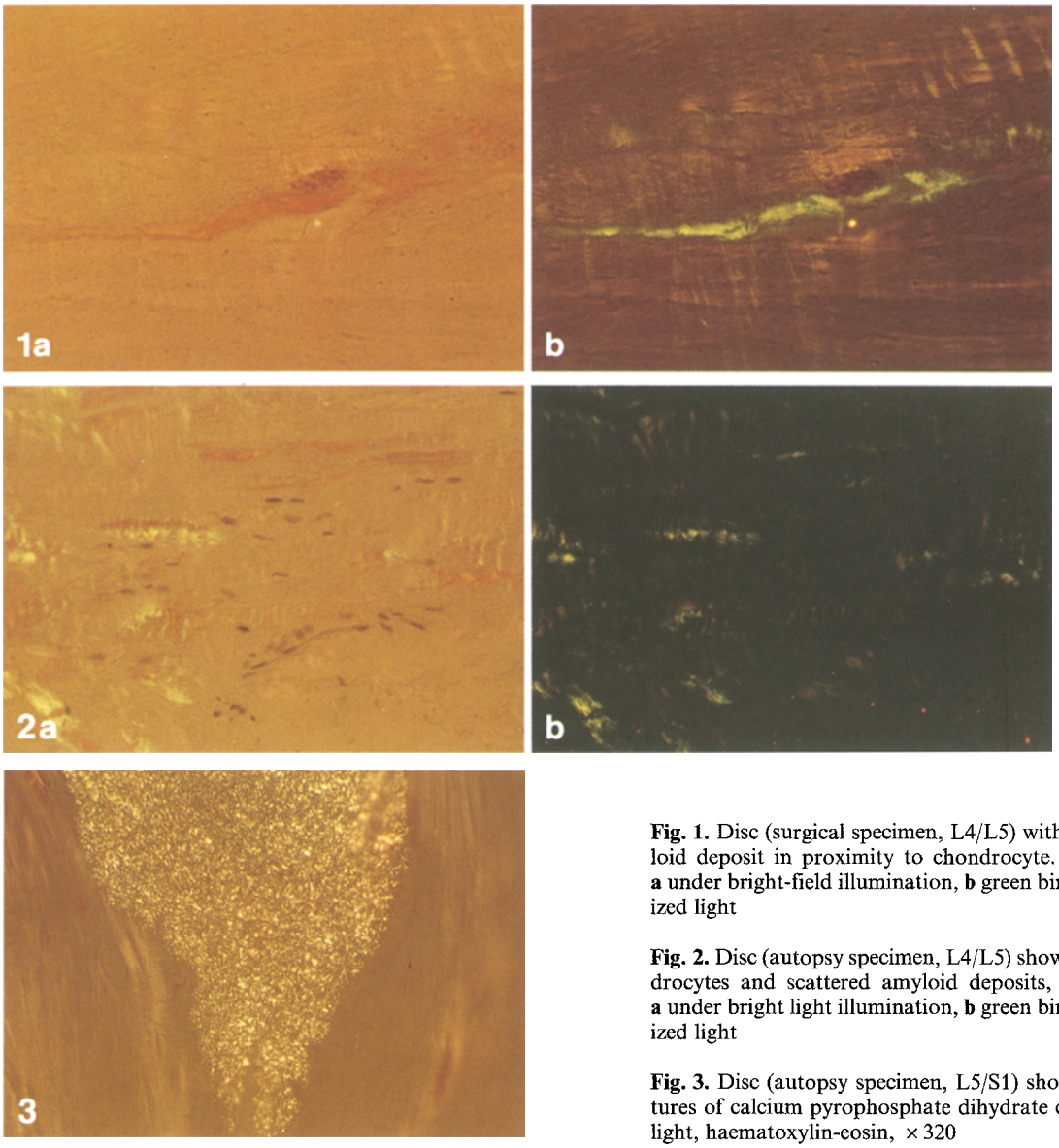


**Fig. 1.** Disc (surgical specimen, L4/L5) with focal streaky amyloid deposit in proximity to chondrocyte. Congo red, ×200. **a** under bright-field illumination, **b** green birefringence in polarized light

**Fig. 2.** Disc (autopsy specimen, L4/L5) showing increased chondrocytes and scattered amyloid deposits, Congo red, ×320. **a** under bright light illumination, **b** green birefringence in polarized light

**Fig. 3.** Disc (autopsy specimen, L5/S1) showing histologic features of calcium pyrophosphate dihydrate crystals in polarized light, haematoxylin-eosin, ×320

showed no specific reaction immunohistologically with the antibodies used.

After exposure to potassium permanganate the amyloid (autopsy and surgery specimens) retained its stainability with alkaline Congo red, including green birefringence in polarized light.

## Discussion

Deposits of amyloid in joints or in their close proximity have been described in cases of patients suffering from generalized amyloidosis with severe arthropathy (Bernhardt and Hensley 1969; Bywaters and Dorling 1970; Kavanaugh 1978; Kurashima et al. 1987) and in patients without the clinical signs of generalized amyloidosis or predisposing diseases (Christensen and Sorensen 1972; Mohr 1976; Teglbjaerg et al. 1979; Goffin et al. 1981; Ladefoged 1982; Ladefoged et al. 1982; Ladefoged 1983; Ladefoged 1986). By electron microscopic studies of intervertebral discs, an accumulation of fibrils showing the ultrastructural feature of amyloid has been demonstrated (Shimizu et al. 1982; Ladefoged 1985; Ladefoged et al. 1986). The interpreting of the results shall not make us forget that the surgical material was selected material. We have shown here that the amount of amyloid deposit in intervertebral discs (from both surgically removed and autopsy specimens) increases with advancing age. These findings are in line with re-

**Table 2.** Amyloid deposits related to age

A Autopsy intervertebral discs (58 patients)

| age (in years) | L3/L4 amyloid | | | | L4/L5 amyloid | | | | L5/S1 amyloid | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | I | II | III | 0 | I | II | III | 0 | I | II | III |
| <41 average: 32.9 SD: 5.1 | 14 | 2 | 0 | 0 | 14 | 2 | 0 | 0 | 14 | 2 | 0 | 0 |
| 41–60 average: 49.6 SD: 6.0 | 11 | 9 | 1 | 1 | 12 | 7 | 3 | 0 | 11 | 7 | 3 | 1 |
| >60 average: 68.3 SD: 8.0 | 0 | 9 | 4 | 7 | 2 | 6 | 4 | 8 | 1 | 8 | 4 | 7 |
| $Chi^2$ test | | $p<0.001$ [a] | | | | $p<0.001$ [a] | | | | $p<0.001$ [a] | | |

B Herniated intervertebral discs (82 patients)

| age (in years) | L4/L5 amyloid | | | | L5/S1 amyloid | | | | all herniated discs amyloid | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | I | II | III | 0 | I | II | III | 0 | I | II | III |
| <41 average: 34.3 SD: 5.1 | 9 | 2 | 0 | 0 | 5 | 5 | 0 | 0 | 15 | 9 | 0 | 0 |
| 41–60 average: 48.7 SD: 5.6 | 3 | 14 | 2 | 0 | 7 | 5 | 1 | 0 | 13 | 23 | 4 | 0 |
| >60 average: 69.6 SD: 7.8 | 1 | 3 | 1 | 3 | 0 | 2 | 2 | 0 | 1 | 6 | 7 | 4 |
| $Chi^2$ test | | $p<0.001$ [b] | | | | $p>0.05$ [b] | | | | $p<0.001$ [a] | | |

Degrees of amyloid deposits: 0 = absent, I = mild, II = moderate, III = severe
SD = standard deviation

[a] the categories II–III and
[b] the categories I–III were combined for statistical evaluation because of the small number of cases

sults of other studies (Wagner and Mohr 1984; Takeda et al. 1984; Ladefoged 1985; Ladefoged et al. 1986). In contrast, this correlation has not been shown for the lumbal disc location L5/S1 of the surgical specimens. We think that this is a consequence of the fewness of cases ($n=27$). It seems unlikely to us that the location L5/S1 predisposes to amyloid deposition since we found almost the same frequency of amyloid deposits in all examined locations in autopsy material. Further studies with a larger number of cases may answer this question definitively.

Our findings on correlation of degenerative changes (ruptures with chondrocyte proliferations) and age were in good agreement to the findings of other authors (Eckert and Decker 1947; Trainer and Andres 1980; Yasuma et al. 1986). It is important to know that ruptured intervertebral discs may show slight degenerative changes not being significantly different from those present in the absence of herniation (Rosai 1989).

Degenerative changes were correlated with amyloid deposits in autopsy but not in surgical specimens. From our autopsy material we cannot rule out that degenerative changes and amyloid deposits are two independent processes which both increase with advancing age. In the material obtained during surgery, the degenerative changes and their relationship to amyloid deposits cannot be determined precisely because these degenerative changes could have resulted at least in part from herniation.

A close relationship between CPPD and amyloid on one hand and CPPD and prior surgery

**Table 3.** Degenerative changes related to age

A Autopsy intervertebral discs (58 patients)

| age (in years) | L3/L4 degenerative changes | | | | L4/L5 degenerative changes | | | | L5/S1 degenerative changes | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | I | II | III | 0 | I | II | III | 0 | I | II | III |
| <41 average: 32.9 SD: 5.1 | 7 | 9 | 0 | 0 | 6 | 10 | 0 | 0 | 4 | 12 | 0 | 0 |
| 41–60 average: 49.6 SD: 6.0 | 0 | 16 | 6 | 0 | 1 | 16 | 4 | 1 | 0 | 19 | 2 | 1 |
| >60 average: 68.3 SD: 8.0 | 0 | 11 | 8 | 1 | 0 | 5 | 13 | 2 | 0 | 5 | 13 | 2 |
| $Chi^2$ test | $p<0.01$[a] | | | | $p<0.001$[a] | | | | $p<0.001$[a] | | | |

B Herniated intervertebral discs (82 patients)

| age (in years) | L4/L5 degenerative changes | | | | L5/S1 degenerative changes | | | | all herniated discs degenerative changes | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | I | II | III | 0 | I | II | III | 0 | I | II | III |
| <41 average: 34.3 SD: 5.1 | 0 | 7 | 3 | 1 | 0 | 7 | 2 | 1 | 0 | 15 | 7 | 2 |
| 41–60 average: 48.7 SD: 5.6 | 0 | 8 | 10 | 1 | 0 | 6 | 6 | 1 | 0 | 22 | 16 | 2 |
| >60 average: 69.6 SD: 7.8 | 0 | 3 | 5 | 0 | 0 | 2 | 2 | 0 | 0 | 7 | 10 | 1 |
| $Chi^2$ test | $p>0.05$[a] | | | | $p>0.05$[a] | | | | $p>0.05$[a] | | | |

Degrees of degenerative changes: 0 = absent, I = mild, II = moderate, III = severe
SD = standard deviation

[a] the categories 0–I and II–III were combined for statistical evaluation because of the small number of cases

on the other was already pointed out in other studies on discs (Weinberger and Myers 1978; Andres and Trainer 1980; Ladefoged 1985; Ladefoged et al. 1986) and joints (Teglbjaerg et al. 1979; Ladefoged 1982; Egan et al. 1982; Ryan et al. 1982; Ladefoged 1983; Ladefoged 1986). We found CPPD with amyloid deposits in the same intervertebral space in only three cases of surgical specimens where there had been a previous operation for a herniated disc. In autopsy material we found CPPD in 13 of 18 discs of six patients. There was only one disc not containing amyloid deposits.

Most interesting are the immunohistochemical results. In the immunohistological examination of surgery and autopsy specimens no reaction was visible. After this, potential methodological reasons for the negative immunohistological typing of amyloid shall be discussed. Amyloid proteins retain their antigenity through histological preparation such as formalin-fixation and paraffin-embedding (reviewed by Shirahama et al. 1984). In the same way, autolysis is not of signification, as discs consist of bradytrophic tissue and as amyloid is relatively resistent to autolysis. The aptitude of the antisera employed for amyloid typing has been pointed out already in previous studies (Linke 1986; Kaa et al. 1986; Stein et al. 1987). Our results exclude amyloid types AA, A$\lambda$, A$\kappa$, AF and $ASc_1$ and AB-amyloid. These findings correlate for amyloid A with those of other authors (Takeda et al. 1984; Ladefoged 1985; Ladefoged et al. 1986) who used the potassium permanganate reaction (Wright et al. 1977) and found that intervertebral disc amyloid as well as amyloid from some

**Table 4.** Amyloid deposits related to degenerative changes

A Autopsy intervertebral discs (58 patients)

| degenerative changes | L3/L4 amyloid | | | | L4/L5 amyloid | | | | L5/S1 amyloid | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | I | II | III | 0 | I | II | III | 0 | I | II | III |
| 0 | 5 | 2 | 0 | 0 | 4 | 3 | 0 | 0 | 2 | 2 | 0 | 0 |
| I | 19 | 13 | 1 | 3 | 22 | 7 | 1 | 1 | 24 | 9 | 2 | 1 |
| II | 1 | 5 | 4 | 4 | 2 | 5 | 6 | 4 | 0 | 6 | 4 | 5 |
| III | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 3 | 0 | 0 | 1 | 2 |
| $Chi^2$ test | $p<0.001$[a] | | | | $p<0.001$[a] | | | | $p<0.001$[a] | | | |

B Herniated intervertebral discs (82 patients)

| degenerative changes | L4/L5 amyloid | | | | L5/S1 amyloid | | | | all herniated discs amyloid | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | I | II | III | 0 | I | II | III | 0 | I | II | III |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| I | 8 | 8 | 1 | 1 | 8 | 5 | 2 | 0 | 19 | 20 | 3 | 2 |
| II | 4 | 10 | 2 | 2 | 4 | 6 | 0 | 0 | 8 | 16 | 7 | 2 |
| III | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 2 | 2 | 1 | 0 |
| $Chi^2$ test | $p>0.05$[a] | | | | $p>0.05$[a] | | | | $p>0.05$[a] | | | |

Degrees of amyloid deposits and degenerative changes: 0 = absent, I = mild, II = moderate, III = severe

[a] The categories II–III (amyloid) and the categories 0–I and II–III (degenerative changes) were combined for statistical evaluation because of the small number of cases

joints (Goffin et al. 1981; Ladefoged 1986) does not consist of amyloid A type. The case with generalized amyloidosis showed amyloid of the A$\lambda$-type in heart, spleen and kidney but not in the intervertebral discs.

These results strongly indicate that the disc amyloid is of a different chemical nature than the known generalized amyloid types. Based on our results, we suppose that the amyloid described here is a form of localized senile amyloidosis. Forms of senile amyloid deposits have been found in several other organs, (e.g. heart atrium, aorta, pancreatic islands, brain, pituitary gland (Cornwell and Westermark 1980; Cornwell et al. 1982; Saeger et al. 1983; Störkel et al. 1983; Westermark et al. 1987a, b; Johannsson et al. 1987; Linke et al. 1988)). Amino acid sequences analysis of different types of senile amyloid showed that these have a different chemical structure (Westermark et al. 1987a, b; Johannsson et al. 1987; Linke et al. 1988). Thus it is thinkable that condrocytes produce a different type of senile amyloid than cells located in the atrium or in the pancreatic islands. Therefore disc amyloid could represent a new amyloid class which manifests in the cartilage. This is, moreover, undermined by the fact that Goffin et al. (1985) in 9 out of 10 cases could not identify immunohistochemically amyloid deposits in cartilages (one case with senile systemic amyloidosis). Using antibodies against serum amyloid A, prealbumin derived amyloid, and light chain amyloid of kappa- and lambda-type. These hypothesis could be verified by amino acid sequence analysis of the different cartilage amyloid proteins which is left for further investigation.

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